RESPIRATORY MEDICINE (1997) 91, 77–82

Body mass index and mortality in patients with severe α_1-antitrypsin deficiency

N. SEERSHOLM

Department of Respiratory Medicine, Bispebjerg Hospital, Copenhagen, Denmark

It appears that patients with advanced stages of chronic obstructive pulmonary disease, and particularly emphysema, lose weight and have higher mortality even after controlling for lung function. In the present study, mortality of α_1-antitrypsin-deficiency patients PiZ as a function of body mass index (BMI) with control for FEV_1, sex and smoking habits was studied. A total of 342 patients participated with a mean follow-up time of 7·6 yr. Ninety patients had BMI under 20 kg m^{-2}, which was the cut-off defining underweight patients. The patients were divided into three groups according to their initial FEV_1 % predicted: <30%, 30–64% and ≥65%. The underweight patients had significantly higher mortality in the two groups with the lowest FEV_1 % predicted. A Cox regression model was applied to control for potential confounders. The risk ratio for the underweight patients was 1·6 (P=0·03) after controlling for FEV_1, age, sex and smoking habits. It is concluded that low body weight is an independent predictor of mortality, but the reason is still unclear.

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Introduction

The hereditary disorder α_1-antitrypsin deficiency (α1ATD) is associated with early onset emphysema and premature death, with smoking being the most important additional risk factor. Impaired lung function in terms of low forced expiratory volume in 1 s (FEV_1) is the most significant predictor of mortality, but current smokers also have a significantly worse prognosis as compared to ex-smokers (1).

It is well known that patients with severe chronic obstructive pulmonary disease (COPD), particularly emphysema, lose weight in advanced stages of the disease. It is also known that in patients with severe COPD and emphysema, low body weight is associated with increased mortality (2), and it has been suggested by Wilson *et al.* (3) that weight loss is a predictor of mortality independent of lung function.

The purpose of the present study was to evaluate mortality as a function of body mass index (BMI) in subjects with severe α1ATD followed for up to 18 yr.

Received 8 December 1995 and accepted 12 April 1996.
Correspondence should be addressed to: N. Seersholm, Munkely 12, DK-2860 Søborg, Denmark.

Patients and Methods

Patients were selected from The Danish α_1-Antitrypsin Deficiency Register in Copenhagen. Since 1978, patients have been registered by physicians throughout Denmark, and once a patient is registered, a family record is obtained and members at risk of having a Z gene are offered an examination of their Pi type. Index cases are patients ascertained because of pulmonary symptoms, and non-index cases are persons ascertained through family studies. More than 3500 family members of index cases have been tested, and by 30 June 1995, the register contained 698 persons with severe α1ATD, of whom 387 were index cases and 311 were non-index cases.

Determination of α_1-antitrypsin Pi type was usually verified by the Department of Clinical Chemistry at Bispebjerg Hospital by isoelectric focusing, as described by Fagerhol and Cox (4). If phenotyping had not been performed, the

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patients were assumed to have phenotype PiZ or PiZ0 if their α_1-antitrypsin serum level was less than 12 μmol l^{-1} (5).

For the index cases, height, weight and lung function measurements (spirometry) were reported by the referring physician. When the non-index cases were ascertained, they were encouraged to contact their general practitioner for assessment of height, weight and spirometry. Spirometry was performed in accordance with European recommendations (6). Predicted values of FEV_1 were calculated according to European reference tables (7). For this study, the first spirometry after the patient entered the registry was used.

Body mass index was calculated as the weight in kilograms divided by the square of the height in metres. The first BMI after the patient entered the registry was used. 'Underweight' was defined as a BMI less than 20 kg m^{-2}.

Information on date of death or emigration was obtained from the Danish Central Population Register (CPR).

Smoking status was defined as follows: smoker, a person who had smoked at least 20 packs of cigarettes or at least one cigarette per day for at least 1 yr in their life time (8); ex-smoker, a person who had abstained from smoking for at least 3 months.

Patients eligible for the present study were identified as Pi-type ZZ or with serum level of α_1-antitrypsin of less than 12 μmol l^{-1}. The patient's status (i.e. dead, alive or emigrated) at the closing date of the study (30 June 1995) should be known, height and weight data should be available and at least one spirometry should have been performed after entry in the register. Furthermore, the patients should be over 20 years old at the closing date.

Of the 698 patients in the register, 112 were PiSZ (99) or had a serum α1AT greater than 12 μmol l^{-1} (13). Thirty-two patients were under 20 years of age at the end of the study. Of the remaining 554 subjects, 111 had insufficient data on weight or height, 92 had no spirometric data and smoking history was unavailable for nine patients, leaving 342 patients for analysis (253 verified PiZ and 89 with α_1-antitrypsin level of less than 12 μmol l^{-1}). There were no differences in age, sex or the number of index cases and non-index cases between the included and excluded patients, but the 212 excluded patients had significantly shorter follow-up times (7·6 *vs.* 4·9 yr; $P<0·001$). Survival analysis revealed a better survival in the included group ($P<0·01$, log-rank test).

Statistics

Cumulative survival probabilities were estimated using the Kaplan–Meier method, and differences in survival were calculated with the log rank test (9). The period of follow-up for survival calculation was taken from the time of the first lung function measurement to the date of death, emigration, lung transplantation or 30 June 1995, whichever came first. The *t*-test was used to evaluate differences in FEV_1, age and follow-up time, and the Chi-square test was used to test dichotomous variables. Cox proportional hazards regression model with time-dependent variables was used to analyse the influence of low BMI on survival, and control for smoking history, FEV_1, gender and age (9).

Results

The study population comprised an equal number of males and females. The mean age at entry was 45 years, and the subjects were followed up for an average of 7·6 yr. During the study period, 107 patients died, three emigrated and 29 received a lung transplant. Ninety (26%) patients had a BMI under 20 kg m^{-2} and were classified as underweight. In Table 1, demographic data of the study population stratified for BMI are shown. The mean follow-up time was 6·8 yr for the underweight patients and 7·8 yr for the patients with BMI over 20 kg m^{-2} ($P=0·07$). Age at entry was similar in the two weight groups. Significantly more women than men were underweight ($P<0·01$), and a significantly higher percentage were current smokers in the underweight group ($P<0·01$). The mean initial FEV_1 % predicted was 38% (SD=21) for the underweight patients, and 57% (SD=30) for the rest ($P<0·001$).

As FEV_1 is a strong determinant of mortality, the patients were classified into three groups based on FEV_1 % predicted: <30%, 30–64% and

TABLE 1. Demographic data of the study population stratified for body mass index

	Total	Body mass index		Weight groups compared (P value)
		<20	≥20	
n (%)	342 (100%)	90 (26%)	252 (74%)	
Sex, men/women	172/170	34/56	138/114	<0·01
Smoking history				<0·01
Current smokers	84 (25%)	35 (39%)	49 (19%)	
Ex-smokers	205 (60%)	44 (49%)	161 (64%)	
Never-smokers	53 (15%)	11 (12%)	42 (17%)	
FEV_1 % predicted, mean (SD)	52·1 (29·5)	37·8 (20·6)	57·2 (30·4)	<0·001
Age at entry (years), mean (SD)	45·5 (10·7)	46·1 (11·9)	45·2 (10·2)	0·5
Follow-up time (yr), mean (SD)	7·6 (4·4)	6·8 (3·6)	7·8 (4·6)	0·07

TABLE 2. Number of dead and censored (emigrated, transplanted or alive at the end of follow-up) patients by body mass index and stratified for FEV_1

		Body mass index		Total
		<20	≥20	
FEV_1 % predicted				
<30%	Dead	26 (70%)	22 (41%)	48 (53%)
	Censored	11 (30%)	32 (59%)	43 (47%)
	Total	37 (100%)	54 (100%)	91 (100%)
30–64%	Dead	18 (39%)	32 (29%)	50 (32%)
	Censored	28 (61%)	78 (71%)	106 (68%)
	Total	46 (100%)	110 (100%)	156 (100%)
≥65%	Dead	1 (14%)	8 (9%)	9 (9%)
	Censored	6 (86%)	80 (91%)	86 (91%)
	Total	7 (100%)	88 (100%)	95 (100%)

≥65%. In Table 2, the number of dead and censored patients by FEV_1 % predicted and BMI are shown. In the group of patients with FEV_1 less than 30% predicted, 41% were underweight compared with 29% in the middle FEV_1 group and 7% in the group of patients with FEV_1 over 65% predicted (P<0·01). Figure 1 shows Kaplan–Meier plots for the group of patients with FEV_1 <30%. Mortality was significantly higher in the underweight group (P=0·01, log-rank test). Also, as shown in Fig. 2, in the group of patients with FEV_1 % predicted between 30 and 64%, underweight patients had significantly higher mortality (P=0·04). For patients with FEV_1 above 65%, there was no significant difference in mortality between the two weight groups (Fig. 3).

This increased mortality in patients with low BMI could be explained by differences in sex and smoking habits. To control for this, a Cox proportional hazards model was applied to the data. Smoking status was entered as two dummy variables: a variable coded 1 for never-smokers and 0 otherwise; and a time-dependent variable coded 1 if the patient quit smoking during the follow-up period or had quit before entering the study. Thus, if a patient quit smoking during the study period, the variable would change from 0 to 1 at the time of smoking cessation. Additional parameters included in the model were FEV_1 % predicted, sex

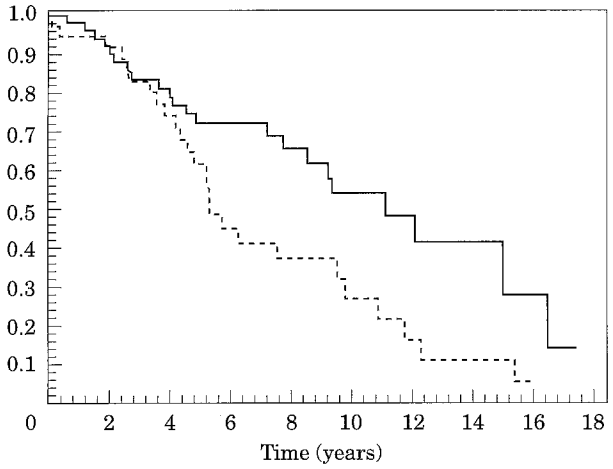

FIG. 1. Kaplan–Meier plots of patients with an initial FEV_1 % predicted less than 30%. ———, body mass index (BMI) ≥20; – – –, BMI <20.

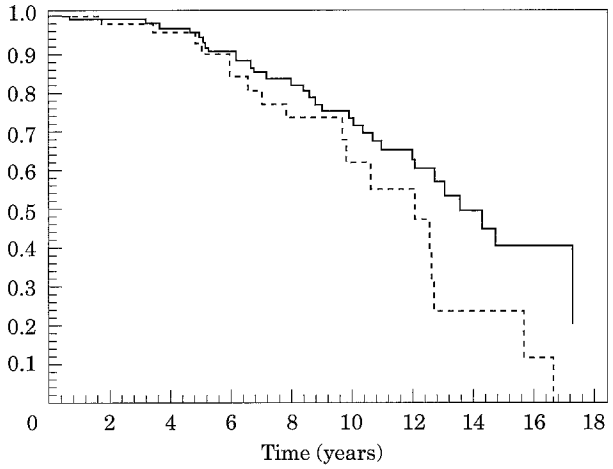

FIG. 2. Kaplan–Meier plots of patients with an initial FEV_1 % predicted between 30 and 64% predicted. ———, body mass index (BMI) ≥20; – – –, BMI <20.

and age. In Table 3, the result of the analysis is shown. Underweight patients had significantly higher mortality with a risk ratio of 1·6 after controlling for FEV_1, smoking habits, sex and age (P=0·03). It is seen that FEV_1 is a very strong risk factor for mortality, with a risk ratio of 8·1 for patients with a FEV_1 less than 30% predicted. Patients who quit smoking had significantly lower mortality compared with patients who continued to smoke, and it was also shown that never-smokers had increased mortality but not significantly. Mortality increased significantly with increasing age, and men had an excess mortality with a relative risk of 1·6 (P=0·03).

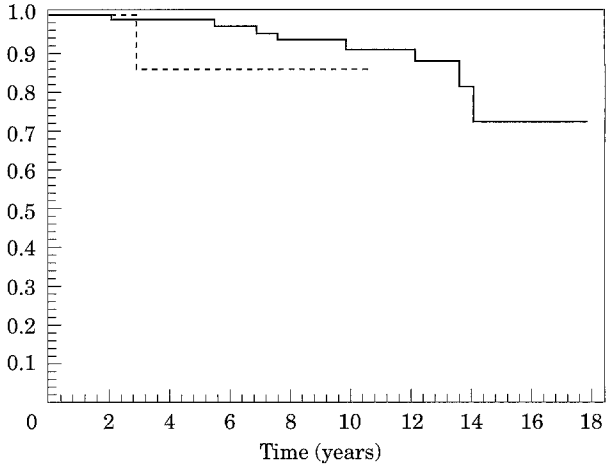

FIG. 3. Kaplan–Meier plots of patients with an initial FEV_1 % predicted more than 65% predicted. ———, body mass index (BMI) ≥20; – – –, BMI <20.

TABLE 3. Cox regression analysis with risk ratio and 95% confidence interval (95% CI)

Parameter	Risk ratio	95% CI	P value
Body mass index			
<20	1·63	1·05–2·53	0·03
≥20	1		
Sex			
Men	1·62	1·06–2·47	0·03
Women	1		
FEV_1 % predicted			
<30	8·09	3·65–17·9	<0·001
30–64	3·26	1·53–6·95	0·002
≥65	1		
Smoking history			
Current smokers	1		
Quitters	0·42	0·26–0·69	<0·001
Never-smokers	1·60	0·85–2·99	0·14
Age	1·06	1·04–1·08	<0·001

Discussion

This study clearly shows that underweight patients with emphysema have a worse prognosis than patients who are not underweight. In a previous study of α1ATD patients, reduced FEV_1 was found to be a strong determinant of mortality. Furthermore, improved survival after smoking cessation with control for FEV_1 was found, and it has also been shown that this was most likely due to slower decline in FEV_1 (1,10).

Therefore, it is important to control for FEV_1 and smoking cessation in evaluating mortality according to weight. Even after controlling for this, and after controlling for gender and age in addition to FEV_1, underweight patients had increased mortality.

The present study is limited by a large number of missing data and it raises the question whether this has caused bias, particularly selection bias. If bias was introduced, the underweight patients with a poor prognosis were more likely to be included in the study than underweight patients with a good prognosis. That is unlikely because the patients were registered consecutively and it was attempted to gather as much information as possible during the registration.

In a study by Wilson *et al.* (3), the mortality of COPD patients followed for up to 3 yr was analysed according to ideal body weight, and stratified for FEV_1 % predicted in three categories: under 35%, 35–46% and 47–60%. A significantly larger mortality of the underweight patients was found in the two high FEV_1 categories alone, and the difference was highest in the FEV_1 group 47–60%. However, the study was limited by a short follow-up time, and no control for smoking habits nor gender.

As opposed to COPD patients (a mixture of patients with airflow obstruction), α1ATD patients develop pure emphysema. Unlike the results from Wilson *et al.*'s study, the present study found an increasing difference in mortality between underweight and normal-weight patients with decreasing FEV_1. This can partly be explained by different study populations and different groups of FEV_1 % predicted. In the present study, one-quarter of the patients had an initial FEV_1 % predicted above 65%, and it was more appropriate to split the study population in broader groups according to FEV_1. The data in the present study has been analysed with stratification for FEV_1 in the groups used by Wilson *et al.* No significantly increased mortality of the underweight patients in the 35–46% group was found, but lack of power may be the main reason for this result.

In the study by Wilson *et al.*, additional lung function parameters such as diffusion capacity (D_LCO), total lung capacity (TLC) and exercise were found to be independently associated with low body weight. It was suggested that underweight patients are more severely affected by the disease than what is reflected by FEV_1, and it was concluded that low body weight is an independent predictor of mortality. The data in the present study are not sufficient for stratification for additional lung function parameters.

As low body weight is a strong predictor of mortality in emphysematous patients, the question arises whether it is possible to revert the process by supplemental feeding. A controlled study by Rogers *et al.* (11) found minor clinical improvements after provision of calorie and protein support resulting in weight gain, but concluded that the intervention was too costly, time-intensive and of limited therapeutic significance.

It is unclear why patients with emphysema lose weight and why low body weight is associated with higher mortality. It has been suggested that the increased work of breathing resulted in increased energy expenditure and negative energy balance, but this does not explain why not all patients with airways disease and increased work of breathing lose weight (12). It has recently been shown that circulating cytokines, such as TNF-α (cachexin), are increased in COPD patients (13). It was suggested that this is due to tissue hypoxaemia and explains why emphysematous patients are more likely to lose weight, since they more often have comprised tissue oxygenation (14). The theory also explains why supplemental feeding is of limited value, and it has been suggested that anti-TNF agents could be used to treat cachectic patients (12).

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